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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,428	01/23/2004	Laura Simmons	11669.120USU1	6080

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,428	SIMMONS, LAURA	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/2/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74 and 82-127* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-74 and 82-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-74 and 82-127 are pending.

2. In view of the amendment filed 10/2/06, the following rejection remains.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-74 and 82-127 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) the structure, i.e. amino acid sequence or the corresponding nucleotide encoding the heavy and light chain variable domain of any and all antibody, any antibody such as humanized antibody, chimeric antibody, monoclonal antibody, human antibody multispecific antibody diabodies an antibody generated by phage display or antigen binding fragment comprising at least any one modified FR for the claimed method as set forth in claims 1, 6, 7, 25-27, 32-34, 38-39, 44-45, 50-51, 60-61, 71-73, 82-86, 96-97, 100, 101, 104-110, 115, (2) which framework region (FR) from which heavy chain or light chain of which antibody to be modified as set forth in claims 1, 6, 12, 14, 16, 17, 18, 23, 29, 38-39, 92, and 117, (3) the type of amino acids to be substituted at position recited in claims 19, 20, 21, 22, 24, 42, 43, 48, 52-54, 56-57, 63-64, and 122-124 and (4) the position or location of the amino acids within the FR or mixture of FR to be substituted as set forth in claims 41, 49, 55, 100, 125, 126, and 127.

The specification discloses only two anti-VEGF antibodies designated VNERK, and Y0317. The specification discloses replacing the human *heavy chain* framework regions 1(FR1) subgroup III consensus sequence of SEQ ID NO: 3 in the specific VEGF antibody with the human *heavy chain* FR1 subgroup I consensus sequence of SEQ ID NO: 1 at those position where the residues differ resulted in increase in antibody yield. The specification also discloses a method for improving the yield of anti-VEGF antibody or humanized VEGF antibody or antigen

binding fragment thereof in cell culture by substituting at least two amino acid residues in FR1 heavy chain of SEQ ID NO: 3 wherein the amino acid residue E at position 6 is substituted for Q and amino acid residue A at position 23 is substituted for K wherein the substitution increases the yield of assembled anti-VEGF antibody about two fold or amino acid residue E at position 1 is substituted for Q, E at position 6 is substituted for Q, L at position 11 is substituted for V, Q at position 13 is substituted for K, L at position 18 is substituted for V, R at position 19 is substituted for K and A at position 23 for K (page 87). The heavy chain FR1 of the modified VEGF antibody is GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO: 18; IgE).

With the exception of the specific amino acid substitutions in the specific anti-VEGF or antigen binding fragment thereof that increase antibody yield in cell culture for the claimed method, the other modification/substitution in any one or more heavy chain FR1, FR2, FR3 and FR4 or mixture thereof in the variable domains of other antibodies are not adequately described. In order to produce any antibody in high yield in culture, the amino acid sequences with the appropriate sequence identifier (SEQ ID NO) or the corresponding polynucleotides of immunoglobulin heavy and light chains variable domains (all six CDRs) including the framework regions are required. Further, the location and the type of amino acids to be substituted within the framework regions of immunoglobulin heavy and light chain of any and all antibody for the claimed method are not adequately described. This is particularly true for amino acid residues at position 21, 22, 24, 25, 86, 87, 89 and 90 in the light chain variable domain of any antibody and/or any amino acid at position 20, 21, 23, 24, 90, 91, 93 and 94 in the heavy chain variable domain of any antibody as set forth in claims 56-57.

With regard to "FR1, FR2, FR3, FR4 and mixture thereof", the specification at page 95-96 discloses that changing the heavy chain FR1 and FR2 of anti-VEGF antibody from human consensus subgroup III residues to the human consensus subgroup I residues increased antibody yield. The specification also discloses changing the heavy chain FR1, FR2 and FR3 of anti-VEGF to human consensus subgroup I increased antibody yield from *E coli* or CHO cells.

The specification does not adequately described the modification in any one or more amino acids within a heavy chain FR4 from any antibody or antigen binding fragment thereof. The specification does not adequately described the modification in any mixture such as heavy chain FR1 and FR4, FR2 and FR4, FR3 and FR4, or all four FR1, FR2, FR3 and FR4 of any

antibody that would resulted in an increase in antibody yield, much less modifying any one or more amino acids in the light chain FR1, FR2, FR3, FR4 or mixture thereof of any antibody.

The specification discloses only a method of producing humanized anti-VEGF and a method of improve the yield of only anti-VEGF antibody or binding fragment thereof by substituting the specific amino acids in the heavy chain FR1, FR2 and FR3 of the specific VEGF antibody, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of antibodies to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 10/2/06 have been fully considered but are not found persuasive.

Applicants' position is the Examiner seems to take the position that written description requires precise sequence information and actual reduction to practice of every embodiment. However, the Federal Circuit has maintained that precise sequence information and actual reduction to practice of every embodiment is not necessary to meet the written description requirement. Applicants further submit that they have provided the sequences of 9 different antibodies and that many other sequences are known to those of skill in the art. Applicants have provided working examples of at least one substitution in a FR region for at least 4 different antibodies. Applicants have described that the location of the amino acids to be substituted are those that when aligned with the corresponding selected human subgroup consensus FR sequence differ from that of the antibody or antigen binding fragment. The amino acid substituted at that position is the amino acid in the corresponding position of the selected subgroup consensus sequence. Thus, Applicants submit that one of skill in the art reading the specification would understand that Applicants were in possession of the claimed subject matter.

In response, the claims encompass a method of producing any antibody or antigen binding fragment in high yield from a host cell.

The specification discloses a method of producing anti-VEGF antibody or antigen binding fragment thereof in high yield from bacterial host cell, comprising the steps of a) aligning

the hypervariable region (HVR1) and/or hypervariable region 2 (HVR2) of the non-human monoclonal antibody to the corresponding HVR1 and/or HVR2 sequences of the human subgroup consensus sequences, b) selecting the human consensus subgroup sequence with the most sequence identity to the HVR1 and/or HVR2 of the non-human monoclonal antibody to provide at least one of the framework region (FR) sequences in the humanized antibody or antigen binding fragment, c) identifying amino acid positions in the FR that differ between the two sequences as the amino acid positions that can be substituted, d) substituting at least one amino acid that differs with an amino acid at the corresponding amino acid position found in the human subgroup consensus sequence, e) expressing a modified variable domain of the antibody or antigen binding fragment thereof comprising at lest one modified framework region (FR) in the host cell, and f) recovering the antibody or antigen binding fragment variable domain comprising the at least one modified FR from the host cell wherein said modified framework region has improved the yield of antibody or antigen binding fragment thereof in cell culture as compared to the unmodified parent antibody or antigen binding fragment thereof, see pages 38. The specification also discloses a method for improving antibody yield by modifying residues at proximal to a Cys residue that forms an interchain disulfide bond, see page 39. The heavy chain residues proximal residues adjacent to a cys residue are 20, 21, 23, 24, 90, 91, 93 and 94. The proximal residues adjacent to a cys residue in the light chain variable domain are 21, 22, 24, 25, 86, 87, 89 and 90, see page 41.

However, the specification does not describe amino acid positions to be substituted such as the ones recited in claims 19, 21, 42, 43, 63, 64, and 122 for anti-VEGF antibody are applicable to a method producing high yield from a host cell for other antibody. Further, it is noted that SEQ ID NO: 14 and 18 are HVR1 amino acid sequences from anti-VEGF antibody. The specification does not disclose that SEQ ID NO: 14 and 18 from anti-VEGF antibody are applicable to other antibody for the claimed method. Although Applicants have described that the location of the amino acids to be substituted are those that when aligned with the corresponding selected human subgroup consensus FR sequence differ from that of the antibody or antigen binding fragment such as the ones recited in claims 19, 21, 42, 43, 63, 64, and 122, the amino acids to be substitute at said location needed to be recite in the claims.

5. The following new ground of rejection is necessitated by the amendment filed 10/2/06.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-74 and 82-127 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-74 and 82-127 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is aligning the hypervariable region (HVR1) and/or hypervariable region 2 (HVR2) of the non-human monoclonal antibody to the corresponding HVR1 and/or HVR2 sequences of the human subgroup consensus sequences.

It is suggested that claim 1 be amended to recite "A method of producing anti-VEGF antibody or antigen binding fragment thereof in high yield from bacterial host cell, comprising the steps of a) aligning the hypervariable region (HVR1) and/or hypervariable region 2 (HVR2) of the non-human monoclonal antibody to the corresponding HVR1 and/or HVR2 sequences of the human subgroup consensus sequences, b) selecting the human consensus subgroup sequence with the most sequence identity to the HVR1 and/or HVR2 of the non-human monoclonal antibody to provide at least one of the framework region (FR) sequences in the humanized antibody or antigen binding fragment, c) identifying amino acid positions in the FR that differ between the two sequences as the amino acid positions that can be substituted, d) substituting at least one amino acid that differs with an amino acid at the corresponding amino acid position found in the human subgroup consensus sequence, e) expressing a modified variable domain of the antibody or antigen binding fragment thereof comprising at least one modified framework region (FR) in the host cell, and f) recovering the antibody or antigen binding fragment variable domain comprising the at least one modified FR from the host cell wherein said modified framework region has improved the yield of antibody or antigen binding fragment thereof in cell culture as compared to the unmodified parent antibody or antigen binding fragment thereof." It is further suggested that other independent claims such as 25, 38, 39, 50, 74, 82, 96, 100 and 104 be amended using claim 1 above as a model.

Claims 1, 25, 39, 50, 74, 82, 96, 100 and 104 are incomplete for failing to achieve the goal set forth in the preamble. The claims should culminate in a phrase such as: "said modified

framework region has improved the yield of antibody or antigen binding fragment thereof in cell culture as compared to the unmodified parent antibody or antigen binding fragment thereof."

Amended claim 35 fails to further limiting the method for preparing a humanized antibody or antigen binding fragment as recited in claim 25. This is because base claim 25 recites expressing a *variable domain*...and recovering the *variable domain* from the host cell. The dependent claim 35 now recites further recovering the full-length heavy chain, the full-length light chain or the full-length heavy chain and the full-length light chain from the culture. It is also noted that the same problem occurs in claim 7.

Amended claim 62 fails to further limiting the method for preparing an antibody or antigen binding fragment as recited in claim 50. This is because base claim 50 recites expressing a *variable domain*...and recovering the *variable domain*...from the host cell. The dependent claim 62 now recites further recovering the full-length heavy chain, the full-length light chain or the full-length heavy chain and the full-length light chain from the culture. Further, the recitation of "a *first* polynucleotide" in claim 60 is ambiguous and indefinite because if there is a first polynucleotide, then it is expected there is a second polynucleotide and it is not clear where is the *second* polynucleotide in claim 60.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

11. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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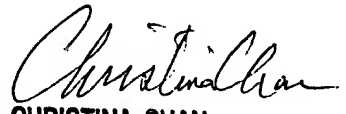
December 8, 2006



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